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The relationship between disease prognosis and serum calcium and corrected calcium levels in COVID-19 patients

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ABSTRACT

Objectives: The present study aimed to evaluate whether low serum calcium (Ca) and corrected calcium (cCa) levels could predict disease prognosis and mortality in patients with COVID-19.

Methods: In this study, we retrospectively enrolled 206 eligible patients with COVID-19, diagnosed at Turkey Kanuni Sultan Süleyman Training and Research Hospital between March 12, 2020 and June 15, 2020.

Results: Serum Ca level was 8.8 ± 0.57 mg/dL and the serum cCa level was 8.99 ± 0.53 in all patients. The patients were divided into two groups, such as hypocalcemic and non-hypocalcemic patients. We observed that serum Ca levels of patients who died were significantly lower than that of surviving patients. A significant negative correlation was found between serum cCa level and albumin level. A significant positive correlation was found between serum cCa level and C-reactive protein, lactate dehydrogenase, ferritin, procalcitonin, troponin, CURB-65 score, and quick Sepsis-related Organ Failure Assessment (q-SOFA) score. Univariate logistic regression analysis revealed that age, respiratory rate, saturation, heart rate, lymphocyte, serum calcium, D-dimer, CURB-65 score, and q-SOFA score were independent predictors of high-risk group of mortality.

Conclusions: This study confirms that the severity of COVID-19 is associated with lower concentrations of serum Ca. The cCa levels were associated with certain prognostic factors. Serum Ca and cCa levels could be an early and helpful marker to improve management of patients with COVID-19. We recommend evaluation of calcium in patients on initial presentation and serial monitoring during hospitalization in order to perform timely and appropriate corrective actions.

Keywords: COVID-19, mortality, calcium, corrected calcium, hypocalcemia

Coronavirus disease-19 (COVID-19), which was first manifested as atypical pneumonia cases in Wuhan, the capital of Hubei province of China in December 2019, was later found to be a new type of coronavirus. The COVID-19 disease is termed SARS-CoV-2 because its etiology resembles the severe acute respiratory syndrome coronavirus (SARS-CoV). COVID-19 disease continues to be a major health con-

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cern throughout the world, including Turkey [1, 2]. Although, COVID-19 disease can usually be manifested as an asymptomatic or mild disease, its clinical course can be severe in some cases. The severe clinical course can be predicted in patients with certain clinical features; however, this cannot be done with absolute certainty. Advanced age, male gender, presence of comorbid diseases (especially hypertension, diabetes mellitus, and coronary artery disease), obesity, hypotension, tachypnea, hypoxia, lymphopenia, thrombocytopenia, hypoalbuminemia, impaired renal function, high levels of C-reactive protein (CRP), D-dimer, procalcitonin, interleukin-6 (IL-6), ferritin, alanine transaminase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH), and the presence of ground glass opacity on tomography have been reported to be poor prognostic factors for the disease [1, 3-11].

SARS-CoV-2 binds to the angiotensin-converting enzyme (ACE)-2 receptor through the S protein and enters the respiratory tract and causes cell damage through cytopathic effect and cytokine release [12]. Calcium (Ca2+) is an important molecule in viral infections for the formation of the virus structure, entry of the virus into the cell, gene expression, virion maturation, and release [13]. In vitro experimental studies and studies on animal models infected with SARS-CoV have demonstrated that the SARS-CoV E gene encodes a small transmembrane protein that is highly expressed during infection and has ion channel activity. It has been reported that these ion channels are permeable to calcium and activate inflammatory pathways through intracellular calcium homeostasis changes, disrupt the host cell system, and facilitate the replication of the virus [14-16]. The similarity between SARS-CoV-2 and SARS-CoV genomes suggests that a similar mechanism may be effective.

Serum Ca level abnormalities are common in hospitalized patients and are known to be associated with mortality [17]. While some studies reported higher mortality in hypocalcemic cases, other studies reported that hypercalcemic cases had higher mortality rates [18, 19]. However, there are no studies that have actually studied this hypothesis in patients with COVID-19. The fact that the calcium molecule plays an active role in the host cell–virus interactions prompt us to think that the differences in calcium levels can cause differences in the effects of the virus on the host cell and can thereby affect the course of the disease. Therefore, this study aimed to investigate the factors affecting the relationship between disease prognosis and mortality with serum Ca and corrected calcium (cCa) levels in patients with COVID-19.

METHODS

Study Design

The protocol of the current study was approved by the ethics committee of Health Sciences University, Kanuni Sultan Süleyman Research and Training Hospital (No: KAEK/2020.06.114). This retrospective study was conducted in the Health Sciences University, Kanuni Sultan Suleyman Research and Training Hospital, Department of Internal Medicine. We enrolled 206 patients diagnosed with COVID-19 between March 12, 2020 and June 15, 2020 in this study.

Patient Characteristics and Data Collection

This retrospective cross-sectional study was carried out utilizing the medical records of patients who were hospitalized in isolated wards with the diagnosis of COVID-19 in a tertiary education and research hospital. In this study, we included patients with positive SARS-CoV-2 RNA detection in throat swab samples and who were diagnosed with COVID-19 according to the World Health Organization (WHO) guidelines. All patients were of Turkish descent.

We recorded the treatments received by the patients, duration of hospitalization, and the disease outcome (survival or nonsurvival). Demographic data of the patients (age, gender, hospital admission complaints, and comorbid diseases) and vital signs at the time of admission (presence of fever, heart rate, percentage of oxygen saturation on room air, and minute-respiration rate) were obtained from the patient's medical record. Laboratory data [complete blood count (CBC), CRP, creatinine, ALT, AST, albumin, calcium, LDH, D-dimer, fibrinogen, ferritin, procalcitonin (PCT), and troponin] and imaging analysis of the patients at the time of admission (presence of lung involvement on chest tomography; and if there is involvement, whether it is unilateral or bilateral and presence of consolidation and ground glass appearance) were obtained from the medical records.

Patients under the age of 18, patients whose serum

Ca level was not checked at the time of hospital admission, pregnant women, breastfeeding women, patients with comorbidities that may affect serum calcium levels (such as primary hyperparathyroidism, hypoparathyroidism, malignancy, multiple myeloma, osteoporosis, granulomatous diseases, and pancreatitis), and patients who were on medications within the last 1 month that could affect serum calcium levels (such as lithium, vitamin D, thiazide diuretics, and bisphosphonates) were not included in this study.

The cCa level (mg/dL) was calculated using the following formula: measured serum Ca level (mg/dL) + 0.8 × [(4-serum albumin (g/dL)]. Patients with serum Ca level or serum cCa level < 8.5 mg/dL were defined as the "hypocalcemic group," and patients with serum Ca level or serum cCa level ≥8.5 mg/dL were defined as the "non-hypocalcemic group."

The CURB-65 score was calculated by considering 1 point for each of the following conditions: confusion, respiratory rate ≥ 30/min, systolic blood pressure < 90 mmHg or diastolic blood pressure < 60 mmHg, BUN >19 mg/dL, and age ≥ 65.

q-SOFA score was calculated by considering 1 point for each of the following parameters: abnormal state of consciousness, respiratory rate ≥ 22/min, and systolic blood pressure ≤ 100 mmHg.

Samples were tested using the WHO recommendations and national guidelines [20].

Laboratory Procedures

Blood samples were obtained prior to treatment and collected into standardized tubes containing EDTA for analysis of CBC parameters and standardized tubes without any anticoagulant for the biochemical analysis. Serum samples that were obtained after centrifugation at 2500 g for 5 min were used directly for the measurements of biochemical parameters.

CBC was analyzed by a Sysmex XT 1800i device (ROCHE-2011, Kobe, Japan). Ca and other biochemical parameters were analyzed by a COBAS 8000 device (ROCHE-2007, Tokyo, Japan).

CRP analysis was performed using the immunoturbidimetric method (ROCHE DIAGNOSTICS HITACHI, Tokyo, Japan).

Plasma fibrinogen was measured by using Clauss method using Fibrintimer II coagulometer and Multifibren U kit (Siemens Healthcare Diagnostics, Germany).

D-dimer analysis was carried out on plasma collected into 3.2% buffered sodium citrate blood tubes (Becton Dickinson, Franklin Lakes, NJ, USA), using Stago coagulation analyzers STA compact Max 3 (Stago, Asnières-sur-Seine, France) and proprietary reagents by immunoturbidimetric method.

Ferritin, PCT, and troponin were measured in VIDAS (BioMerieux Inc. France)) device by electrochemiluminescence immunoassay (ECLIA) method.

Oxygen saturation was measured every 4 hours using a digital saturometer. Oxygen flow was calculated to obtain oxygen saturation between 90% and 94%.

Computed Tomography (CT)

We used a multidetector CT scanner (Toshiba Aquilon; Toshiba, Inc., Tokyo, Japan) with the following parameters: tube voltage, 120 kV; tube current, 110 mAs (automatic adjustment); rotation time, 0.5 second; section thickness, 0.75 mm; collimation, 0.6 mm; pitch, 1; matrix, 512 × 512; and inspiration breath hold. Axial, sagittal, and coronal reformatted images were created with a slice thickness of 3-mm.

Analysis of RT-PCR Test

SARS-CoV-2 was detected by real time polymerase chain reaction method in oropharyngeal/nasopharyngeal swab samples.

Statistical Analysis

SPSS 21.0 program was used for data analysis. Nominal variables were expressed as number and percentage, whereas numeric variables were represented as mean ± standard deviation or median. Kolmogorov–Smirnov test was performed to determine whether the continuous variables were normally or non-normally distributed. Normally distributed independent continuous variables were compared with the independent t-test, whereas non-normally distributed independent continuous variables were compared with the Mann–Whitney U test among the groups. A univariate regression analysis was performed to observe the effects of possible parameters on mortality. In order to evaluate the relationship between serum Ca level and mortality, we determined a cut-off value for serum Ca level by the receiver operating characteristic (ROC) analysis. A two-tailed p value of < 0.05 was considered to be statistically significant. In the power

analysis made through the GPower 3.1.9.4 program, it has been determined that the achieved power value (1-β err prob) of the study is 1.

Table 1. Demographic data of patients

Gender	n	%
Male	113	54.9
Female	93	45.1
Complaint of admission time		
Cough	148	71.8
Fever	114	55.3
Weakness	96	45.1
Shortness of breath	88	42.7
Myalgia	36	17.5
Sore throat	15	7.3
Headache	9	4.4
Diarrhea	5	2.4
Treatment options		
Hydroxychloroquine	205	99.5
Azithromycin	195	94.7
Oseltamivir	120	58.3
Favipiravir	27	13.1
Additional antibiotic	40	19.4
Intravenous fluid replacement	34	16.5
Oxygen support	83	40.3
Enoxaparin sodium	126	61.2
Comorbid diseases		
Hypertension	73	35.4
Type-2 Diabetes mellitus	43	20.9
Chronic obstructive pulmonary disease	25	12.1
Coronary artery disease	25	12.1
Immunological disease	5	2.4
Cerebrovascular disease	3	1.5
Tomography findings		
Unilateral involvement	25	12.1
Bilateral involvement	158	76.7
No pulmonary involvement	23	11.2
Ground glass opacity	175	85
Presence of consolidation	105	51
Outcome		
Recovered	194	94.2
Died	12	5.8

RESULTS

In this study we included 206 patients (113 males, 93 females) with a mean age of 55.1 ± 15.7 years (range: 19-92 years). The demographic data of the patients are presented in Table 1.

The most common complaint of these patients was cough, the next common complaint being high fever. The most common comorbid diseases were determined as hypertension, type-2 diabetes mellitus, obstructive pulmonary diseases, and coronary artery disease. The number of patients with at least 1 comorbid disease was 104 (50.5%), the number of patients with at least 2 comorbid diseases was 60 (29.1%), whereas the number of patients with 3 or more comorbid diseases was 19 (9.2%). Chest tomography demonstrated bilateral lung involvement (76.7%) and ground glass appearance (85%) in majority of the patients, consolidation (51%) was observed in nearly half of the cases, whereas 23 patients demonstrated no signs of pneumonia. Most of the patients received hydroxychloroquine and azithromycin therapy, and more than half of the patients also received enoxaparin sodium and oseltamivir. The mean duration of hospitalization of the patients was 7.1 ± 3.3 days (2-19 days). Twelve patients (5.8%) succumbed to the disease.

When all patients were taken into consideration, serum Ca level was found to be 8.8 ± 0.57 mg/dL and serum Ca level was found to be 8.99 ± 0.53 mg/dL. The results obtained when the patients were grouped and compared as hypocalcemic and nonhypocalcemic are presented in Table 2.

The serum Ca levels of patients who died were significantly lower than those of patients who survived (8.4 ± 0.64 vs. 8.83 ± 0.56, $p = 0.013$), but there was no significant difference between serum cCa levels (9.08 ± 0.6 vs. 8.98 ± 0.53, $p = 0.544$). No significant difference was found between serum Ca levels of patients with and without pneumonic infiltration (8.80 ± 0.55 vs. 8.83 ± 0.71, $p = 0.844$), with at least one comorbid disease or no comorbid disease (8.85 ± 0.60 vs. 8.75 ± 0.54, $p = 0.188$), and who were using ACE inhibitors/angiotensin II receptor blockers or who did not use these drugs (8.93 ± 0.64 vs. 8.77 ± 0.55, $p = 0.140$).

The results obtained in the univariate regression analysis for the parameters predicted to have an effect

Table 2. Comparison of the patients in terms of serum calcium and corrected serum calcium levels

	Serum calcium		*p* value	Corrected serum calcium		*p* value
	< 8.5mg/dL (n = 57)	≥ 8.5mg/dL (n = 149)		< 8.5mg/dL (n = 42)	≥ 8.5mg/dL (n = 164)	
Age (year)	55.01 ± 15.91	55.2 ± 15.78	0.94*	52.02 ± 15.81	55.95 ± 15.72	0.104**
Sex (F/M)	22/35	71/78	0.275#	17/25	76/88	0.603#
Hospitalization duration (day)	7.59 ± 3.68	7.03 ± 3.28	0.32**	7.19 ± 3.46	7.18 ± 3.39	0.922**
Respiratory rate (min)	19.64 ± 2.87	19.48 ± 2.62	0.956**	19.66 ± 2.97	19.49 ± 2.61	0.897**
Heart rate (min)	89.43 ± 11.87	85.47 ± 9.88	0.016**	87.69 ± 12.06	86.28 ± 10.19	0.617**
Saturation (%)	92.05 ± 10.93	93.81 ± 5.65	0.569**	92.57 ± 12.28	93.51 ± 5.72	0.43**
Calcium (mg/dL)	8.16 ± 0.29	9.05 ± 0.45	< 0.001*	8.15 ± 0.34	8.97 ± 0.49	< 0.001*
Corrected serum calcium (mg/dL)	8.56 ± 0.43	9.15 ± 0.47	< 0.001*	8.36 ± 0.32	9.15 ± 0.45	< 0.001*
WBC (103µ/L)	6.31 ± 2.66	7.04 ± 3.07	0.093**	5.65 ± 2.32	7.14 ± 3.06	0.001**
Hb (g/dL)	13.74 ± 7.97	13.18 ± 1.64	0.297**	12.76 ± 2	13.48 ± 4.82	0.368**
Neutrophil (103µ/L)	4.31 ± 2.19	4.92 ± 4.91	0.529**	3.72 ± 1.78	5.01 ± 4.74	0.017**
Lymphocyte (103µ/L)	1.335 ± 0.84	1.77 ± 1.39	0.001**	1,39±0,73	1.72±1.37	0.087**
Platelet, (103µ/L)	213.63 ± 80.34	258.45 ± 100.8	0.001**	199.92 ± 54.69	257.9 ± 102.5	< 0.001**
CRP (mg/L)	65.48 ± 54.67	45.35 ± 53.28	0.001**	51.32 ± 42.98	50.82 ± 56.94	0.251**
Creatinine (mg/dL)	1.33 ± 1.34	0.88 ± 0.32	0.008**	1.36 ± 1.52	0.91 ± 0.37	0.189**
ALT (U/L)	50.84 ± 173.31	32.21 ± 26.64	0.692**	27.19 ± 17.7	39.97 ± 104.6	0.326**
AST, (U/L)	47.07 ± 120	30.85 ± 21.04	0.07**	31.73 ± 12.90	36.26 ± 73.3	0.112**
Albumin, (g/L)	3.49 ± 0.5	3.87 ± 0.43	< 0.001*	3.74 ± 0.46	3.73 ± 0.49	0.698*
LDH (U/L)	312.8 ± 106.17	271.9 ± 90.87	0.01*	299.7 ± 92.9	279.8 ± 98.17	0.263*
D-dimer (mg/L)	1.81 ± 5.22	1.17 ± 2.84	0.637**	1.04 ± 2.13	1.42 ± 3.93	0.409**
Fibrinogen (mg/dL)	428.2 ± 136.3	420.1 ± 150.9	0.378**	388.1 ± 75.7	431.4 ± 158.2	0.559**
Ferritin (mg/mL)	664.2 ± 177.8	334.1 ± 376.9	0.016**	724.69 ± 212.8	356.1 ± 390.8	0.277**
Procalcitonin (mg/mL)	0.38 ± 1.04	0.08 ± 0.15	0.007**	0.20 ± 0.53	0.15 ± 0.59	0.869**
Troponin (mg/mL)	0.024 ± 0.042	0.016 ± 0.025	0.498**	0.020 ± 0.035	0.017 ± 0.03	0.881**
CURB-65 score	0.85 ± 0.93	0.51 ± 0.82	0.011*	0.64 ± 0.9	0.6 ± 0.86	0.795*
q-SOFA score	0.66 ± 0.8	0.45 ± 0.78	0.089*	0.5 ± 0.7	0.51 ± 0.81	0.894*

*: Student T test, **: Mann Whitney U test, #: Ki kare test

WBC = White Blood Cell, Hgb = Hemoglobin, CRP = C-reactive protein, ALT = Alanine transferasis, AST = Aspartat transferasis, LDH = Lactat dehidrogenasis, q-SOFA = Quick Sepsis-related Organ Failure Assessment

on mortality are presented in Table 3. When incorporated into the univariate analysis, age, respiratory rate, saturation, heart rate, lymphocyte, serum Ca, D-dimer, CURB-65 score, and q-SOFA score remained as significant predictors of mortality. CRP, ferritin, corrected calcium and PCT were not associated with mortality. In the correlation analysis, a positive correlation was observed between serum Ca level and lymphocyte (r: 0.14, $p = 0.045$), platelet (r: 0.262, $p < 0.001$), and albumin (r: 0.436, $p < 0.001$); and a negative correlation was found between serum Ca level and CRP (r: −0.291, $p < 0.001$), LDH (r: −0.335, $p < 0.001$), creatinine (r: −0.219, $p = 0.002$), ferritin (r: −0.305, $p < 0.001$), procalcitonin (r: −0.237, $p = 0.001$), and CURB-65 score (r: −0.148, $p = 0.033$). There was a positive correlation between serum cCa level and CRP (r: 0.23, $p = 0.003$), LDH (r: 0.252, $p = 0.002$), ferritin (r: 0.304, $p < 0.001$), procalcitonin (r: 0.241, $p = 0.002$), troponin (r: 0.381, $p < 0.001$), CURB-65 score (r: 0.205, $p = 0.008$), and q-SOFA score (r: 0.176, $p = 0.024$). On the contrary, there was a negative correlation between cCa level and albumin level (r: −0.303, $p < 0.001$).

Using the ROC analysis, the cut-off value of

Table 3. Univariate regression analysis for parameters predicted to have an effect on mortality

	Univariate		
Variable	**OR**	**95% CI**	***p* value**
Age	0.927	0.885-0.970	**0.001**
Respiratory rate, min	0.672	0.549-0.822	**< 0.001**
Saturation, %	1.049	1.005-1.094	**0.028**
Heart rate, min	0.932	0.887-0.980	**0.006**
Lymphocyte, 103µ/L	3.064	1.038-9.046	0.043
CRP, mg/mL	0.992	0.984-1.001	0.07
Serum calcium, mg/dL	3.960	1.328-11.806	**0.014**
Corrected serum calcium, mg/dL	0.719	0.250-2.068	0.541
D-dimer, mg/L	0.871	0.83-0.970	**0.012**
Ferritin, mg/mL	0.999	0.998-1.000	0.251
Procalcitonin, mg/mL	0.64	0.378-1.096	0.105
CURB-65 score	0.222	0.111-0.447	**< 0.001**
q-SOFA score	0.094	0.032-0.275	**< 0.001**

serum Ca level to examine the relationship between serum Ca level and mortality was determined as > 8.3 mg/dL. As presented in fig.1, mortality was significantly lower if serum Ca was > 8.3 mg/dL ($p = 0.028$, AUC: 0.681, sensitivity: 79.9%, specificity: 50%).

DISCUSSION

Since there is a high prevalence of hypocalcemia in COVID-19 patients and also due to the fact that hypocalcemia helps in predicting the need for hospitalization, it is recommended that Ca should always be evaluated initially during hospitalization to identify more severe patients [21-23]. We observed that serum Ca levels of the patients who died were significantly lower than that of the patients who survived. Furthermore, there was a significantly lower mortality in patients with serum Ca > 8.3 mg/dL (sensitivity: 79.9%, specificity: 50%) according to the ROC analysis. This study revealed that serum Ca level is a good prognostic parameter in COVID-19 patients and is an independent determinant for mortality. Patients with hypocalcemia have worse prognostic parameters. Moreover, cCa levels were associated with certain prognostic factors.

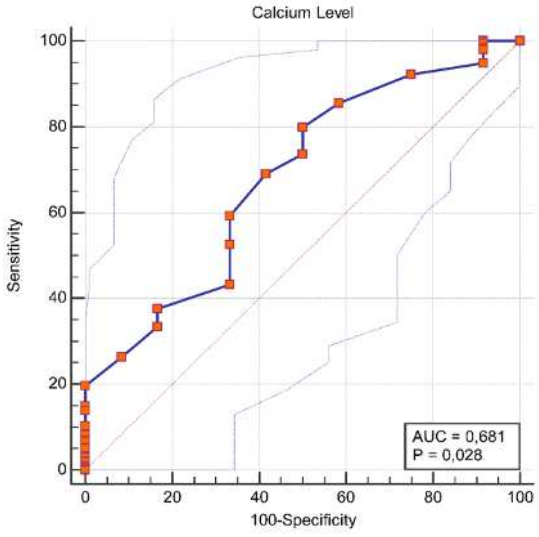

Fig. 1. ROC analysis for serum calcium.

Sun *et al*. [21] reported that the prognostic parameters of patients with COVID-19 with hypocalcemia are worse and the rates of organ failure, septic shock, and mortality are higher. In addition, they stated that the serum Ca level was associated with the severity and prognosis of the disease. In the same study, it was reported that there was a positive correlation between serum Ca and lymphocyte, albumin and SpO2; and a negative correlation between serum Ca, CRP, and D-dimer and that serum Ca levels of patients who died were lower [21]. In another study which included 585 patients who visited the emergency department with suspicion of COVID-19, patients who were diagnosed with COVID-19 and who were not diagnosed with

COVID-19 were evaluated for serum total and ionized Ca, and it was reported that serum total Ca and ionized Ca levels were lower in COVID-19 patients. It has been stated that the total Ca and ionized Ca levels decrease in COVID-19 patients as the age increases, and these values are lower in the male gender [22]. In a retrospective cohort study, it was reported that a high rate of hypocalcemia was detected in patients with COVID-19 at the time of presentation, and this was more common in male and patients with advanced age [23]. In the same study, it was stated that serum Ca levels of patients requiring hospitalization were lower than those not requiring hospitalization, and that serum Ca levels after hospitalization were closely associated with both, death and transfer to the intensive care. Bossoni *et al*. [24] reported severe hypocalcemia in a woman with COVID-19 disease who had underwent thyroidectomy and suggested Ca evaluation and monitoring in all hospitalized patients with COVID-19 infection. Another study reported that calcium, sodium, and potassium concentrations were significantly lower in patients with severe COVID-19 [25]. Cao *et al*. [26] observed that 65.4% of patients with COVID-19 had decreased serum Ca levels. Compared with the non-intensive care unit (ICU) patients, the patients admitted to the ICU were more likely to have low serum calcium (100% vs 61.4%). According to their results, as the Ca levels decreased, the severity of the disease increased. Ca2+ levels and/or Ca2+ channels may play a role in endocytosis and infection of SARS-Cov-2. Further studies are warranted to characterize the functional importance of this potential pathway [26].

However, there are conflicting results on the studies of calcium [18, 19]. Additional clinical information is required to interpret these abnormalities, including fluid status, serum albumin, and ionized calcium concentrations. Therefore, we also evaluated the serum cCa levels in this study. In the present study, serum Ca levels of the patients who died were significantly lower than that of patients who survived. Low serum Ca levels in our study are probably related to the high prevalence of hypovitaminosis D in Turkey, and this may be a predisposing factor in our study population [27]. In the correlation analysis, there was a weak/moderate positive correlation between serum calcium level and lymphocyte, platelet and albumin; and there was a significant weak/moderate negative correlation between serum calcium level and CRP, LDH, creatinine, ferritin, PCT, and CURB-65 score. However, we could not find any significance in this regard with respect to cCa levels. Khamis *et al*. [28] found a relationship between low cCa level and high mortality in patients with COVID-19 who were hospitalized. A total of 38% of the hospitalized patients were admitted to the ICU. This difference may be due to the fact that there were no patients in our sample who were hospitalized in the ICU. On the other hand, in our study, a significant negative correlation was observed between serum cCa level and albumin level; and a weak/moderate positive correlation was found between serum cCa level and CRP, LDH, ferritin, PCT, troponin, CURB-65 score, and q-SOFA score. These results show that cCa levels are associated with certain prognostic factors.

In the present study, univariate logistic regression analysis revealed that age, respiratory rate, saturation, heart rate, lymphocyte, serum Ca, D-dimer, CURB-65 score, and q-SOFA score were independent predictors of high-risk group of mortality. These results demonstrate that there is a higher risk of hypocalcemia associated with COVID-19 disease. As in other studies, our study also showed that advanced age, respiratory rate, saturation, heart rate, lymphocyte, serum Ca, D-dimer, CURB-65 score, and q-SOFA score were risk factors for mortality in patients with COVID-19 [4, 29-33]. In a retrospective cohort study, Zhou *et al*. [4] identified several risk factors of death in adults in Wuhan who were hospitalized with COVID-19. Similar to our results, in particular, advanced age, D-dimer levels >1 μg/mL, and higher SOFA score on admission were associated with higher odds of in-hospital mortality. Additionally, elevated levels of blood IL-6, high-sensitivity cardiac troponin I, LDH, and lymphopenia were more common in severe COVID-19 patients.

CONCLUSION

In conclusion, the results of this study reveal that serum Ca level in COVID-19 patients is a good prognostic parameter and an independent predictor for mortality, hypocalcemic patients have worse prognostic parameters, and there is a moderate/good correlation between serum Ca level and other parameters

previously reported as prognostic factors for COVID-19. Our results indicate that Ca and cCa assessment should be conducted upon patient initial presentation and disturbances in Ca and cCa levels should be monitored throughout the course of the disease in order to perform timely and appropriate corrective actions. Further research based on larger prospective cohort studies is necessary to confirm the findings presented in this study and to establish the clinical significance of our findings.

Authors' Contribution

Study Conception: İE, HÖ, MB, İKU, AÇ, RG; Study Design: İE, RG, AK, HU, ÖT; Supervision: AK, HU, ÖT; Funding: İE, MB, AÇ, RG; Materials: İE, MB, AÇ, RG; Data Collection and/or Processing: İE, MB, AÇ, RG; Statistical Analysis and/or Data Interpretation: İE, RG, AK, HU, ÖT; Literature Review: İE, HO, MB, İKU, AÇ, RG; Manuscript Preparation: İE, RG, AK, HU, ÖT and Critical Review: İE, AK, HU, ÖT.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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